JAN 13 2004

WILMER, CUTLER & PICKERING
2445 M STREET, N.W.
WASHINGTON, DC 20037-1420

TELEPHONE +1 (202) 663 6000
FACSIMILE +1 (202) 663 6363
WWW.WILMER.COM

WASHINGTON
NEW YORK
BALTIMORE
NORTHERN VIRGINIA
LONDON
BRUSSELS
BERLIN

NEIL J. KING
(202) 663-6061
NEIL.KING@WILMER.COM

BY OVERNIGHT DELIVERY

January 13, 2004

Dr. C. W. Jameson
Report on Carcinogens Group
National Toxicology Program
79 T.W. Alexander Drive
Room 3118
MD EC-14
Research Triangle Park, NC 27709

Re: Public Meeting To Discuss the Review Process and the Listing/Delisting Criteria Used for the Report on Carcinogens: 68 Fed. Reg. 67692 (December 3, 2003)

Dear Dr. Jameson:

I am enclosing herewith an original and two copies of the Comments of the Nickel Producers Environmental Research Association and Inco United States, Inc. on the above-referenced matter. Concurrently, I am sending an electronic version of these Comments in pdf format to Ms. Anna Lee Sabella by e-mail. This should ensure that the Comments are received in time to be distributed to the panel conducting the January 27-28 Public Meeting and posted on the NTP RoC web site prior to the meeting—and to be made available to attendees at the Public Meeting,

Thank you for your attention to this matter. If you have any questions regarding these Comments, please let me know.

Very truly yours,
[Redacted]

Neil J. King

Enclosures

BEFORE THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL TOXICOLOGY PROGRAM

Public Meeting To Discuss the Review Process and the Listing/Delisting Criteria Used for the Report on Carcinogens, 68 Fed. Reg. 67692 (December 3, 2003)	)

COMMENTS OF

THE NICKEL PRODUCERS ENVIRONMENTAL RESEARCH ASSOCIATION

and

INCO UNITED STATES, INC.

Communications Regarding These Comments Should Be Directed to:

Neil J. King
Wilmer, Cutler & Pickering
2445 M Street, N.W.
Washington, D.C. 20037-1420
Phone: (202) 663-6061
Fax: (202) 772-6061
e-mail: neil.king@wilmer.com

January 13, 2004

The Nickel Producers Environmental Research Association ("NiPERA") and Inco United States, Inc. are pleased to submit these Comments in response to the request by the National Toxicology Program ("NTP") for an expression of views on the process used to make decisions regarding the listing and delisting of substances in the Report on Carcinogens ("RoC") and on the listing criteria themselves. 68 Fed. Reg. 67692 (December 3, 2003). NiPERA is an association of the western world's principal nickel producers. Inco United States, Inc. is a wholly-owned subsidiary of Inco Limited, a Canadian corporation that is a member of NiPERA. Inco and NiPERA are interested in the issues to be considered at NTP's upcoming Public Meeting on this subject because of our recent experience with NTP's evaluation of nickel metal and nickel compounds in connection with the preparation and publication of the 10th RoC. At the end of the process, nickel metal was listed as "reasonably anticipated to be a human carcinogen," and nickel compounds (without differentiation) were listed as "known to be a human carcinogen."

On the basis of this recent experience, we have several suggestions for improvements in the RoC listing process and the criteria that are applied. We also believe modifications should be made in the discussion of listed substances that appears in the body of the RoC. In our view, the discussion of nickel metal and nickel compounds in the 10th RoC was unbalanced and misleading in a number of respects and failed to meet the objectivity and science quality criteria of the Data Quality Act[1/]

1/ Section 515 of the Treasury and General Government Appropriations Act for Fiscal Year 2001 (P.L. 106-554).

and the implementing Guidelines issued by the Office of Management and Budget,[2/] the Department of Health and Human Services,[3/] and the National Institutes of Health.[4/] Accordingly, we submitted a request for correction of information, which currently is awaiting a decision on appeal.

Based on our experience with the 10th RoC (and with the earlier consideration of nickel compounds in connection with the 9th RoC), we offer the following suggestions:

1. Background Documents. Listing determinations for the RoC are made on the basis of a "draft" background document for the nominated substance that is prepared by NTP (generally with the assistance of a consultant) prior to review by the NIEHS/NTP RoC Review Committee ("RG1").[5/] RG1 consists of scientists from NIEHS/NTP staff who may or may not have particular expertise regarding the nominated substance. Yet, if RG1 determines that the "draft" background document "is adequate for use in reviewing the nomination and applying the criteria for listing in the RoC . . . . the background document is considered the final document of record and is placed on the NTP RoC Web site."[6/] Up to that point, no one outside NIEHS/NTP has had a chance to review or comment upon the "draft" background document. Although comments on the "draft" document are invited thereafter, the "draft" background

---

2/ 67 Fed. Reg. 8452 (February 22, 2002).

3/ Guidelines for Ensuring the Quality of Information Disseminated to the Public (http://www.hhs.gov/infoquality/part1A-9-20.htm).

4/ Guidelines for Ensuring the Quality of Information Disseminated to the Public (http://www.hhs.gov/infoquality/NIHinfo2.htm).

5/ *See* 68 Fed. Reg. at 67694.

6/ *Id.*

document is never revised. Instead, it is distributed to all groups up the chain of review in its original form and remains on the NTP Web site unchanged, regardless of how telling the comments and criticisms of the "draft" background document may be. Given the central role that the background document plays in the review and listing process, this procedure is not acceptable. We suggest it be modified as follows.

- Interested members of the public should be given an opportunity to review and comment on the "draft" background document before RG1 determines whether it is adequate for reviewing the nominated substance and applying the listing criteria.

- NTP should convene a panel of independent scientists who have special expertise with the nominated substance to review and comment on the "draft" background document before it goes to RG1 as a "final draft." Comments on the "draft" background document submitted by members of the public should be furnished to the panel of independent scientists at the same time they are provided with the "draft" background document itself, so that panel members will have the benefit of the public's views and information as they conduct their own review of the draft.

- When the expert panel has completed its review of the "draft" background document, a report containing the panel members' comments/critique of the "draft" background document should be prepared and sent to NTP.

- NTP should then respond to the public comments and to those of the panel by revising the "draft" background document to reflect the comments that have been made by the public and the panel and/or by explaining why any significant comments not reflected in the revised document were rejected. Only then should the background document be provided to RG1 and placed on NTP's Web site.

2. Route of Exposure Considerations. The listing criteria should be revised to place a greater emphasis on whether the nominated substance poses a carcinogenic hazard via routes of exposure that are relevant to the U.S. population. Under Section 301(b)(4) of the Public Health Service Act, as amended, the RoC is supposed to address known or reasonably anticipated carcinogens "to which a significant number of persons residing in the United States are exposed." Obviously, the concern is with

those exposures of the U.S. population that present a potential risk of cancer. If a substance has been associated with an increased cancer risk only via a route of exposure that has no relevance for U.S. residents, while studies via relevant routes of exposure (*i.e.*, inhalation, ingestion, and dermal contact) indicate the absence of a carcinogenic hazard, we question whether the substance can properly be viewed as presenting a "known" or "reasonably anticipated" cancer hazard to persons residing in the United States. In our view, including such a substance in the RoC is misleading.

NTP seems to recognize this point—at least implicitly—since it claims that conclusions regarding carcinogenicity are based, *inter alia*, on information regarding route of exposure.[7/] In practice, however, the significance of route of exposure is largely ignored. It appears that if a substance has been found to cause cancer through the most exotic route of exposure in rodents, it would be listed in the RoC even though human and animal studies by routes of exposure having actual relevance to the U.S. population do not show an increased risk of cancer. Indeed, the negative (or "non-positive") studies by relevant routes of exposure are unlikely to receive any mention whatsoever in the RoC. Instead, a highly skewed picture of study results likely would be presented—with only the positive findings (even though they may involve exotic routes of exposure) being discussed. In our view, this approach undercuts Congress' objective in directing publication of the RoC (*i.e.*, to identify cancer hazards associated with actual exposures of U.S. residents), and it does a disservice to readers of the document.

To remedy this problem, the RoC listings should specify, where appropriate, the route(s) of exposure of the chemical to which the classification applies and those for

---

7/ *See* 68 Fed. Reg. at 67695.

which the classification is inapplicable or uncertain. By the same token, the RoC's summary profile for the substance should discuss whether a carcinogenic hazard has been found in studies involving each of the three principal routes of human exposure to the chemical (inhalation, oral ingestion, and dermal contact). This would provide much needed perspective for readers of the RoC and would avoid giving rise to concerns that are not justified by the nature of exposures in the U.S. At the very least, if a substance is listed as a "known" or "reasonably anticipated" human carcinogen despite the fact that human or animal studies involving the relevant routes of exposure are negative (or "non-positive"), these negative studies should be highlighted and discussed in the RoC's summary profile for the chemical. Otherwise, readers of the RoC will be left with a misleading impression of the hazard that their actual exposures to the chemical may present.

3. Physical Form of the Substance. As with route of exposure, the RoC listings should specify, where appropriate, the physical form(s) of the chemical to which the classification applies and those for which the classification is inapplicable or uncertain. A good illustration of this would be powder forms of a particular metal (which might be carcinogenic via inhalation) versus massive forms of the same metal (which cannot be inhaled and, therefore, would not be carcinogenic). For example, even if metallic nickel powder can "reasonably be anticipated to be a human carcinogen" (which we dispute), the massive forms of metallic nickel with which U.S. residents tend to come in contact (*e.g.*, in nickel-plated products) would not pose a cancer hazard because they cannot be inhaled. This distinction is ignored in the RoC. It should not be. Where the physical form of a chemical is relevant to its carcinogenic potential, that

fact should be reflected both in the listings themselves (by specifying the form of the chemical to which the listing applies) and in the RoC's summary profile for the chemical.

4. Speciation. Finally, we urge NTP to be more attentive to species-specific differences in assessing the carcinogenic potential of a chemical group, such as the compounds of a particular metal. It is all too easy to reason that the metal ion is the carcinogenic agent and that all compounds of the metal contain the metal ion; therefore, if any compound of the metal has been found to be carcinogenic, all compounds of the metal must be carcinogenic. NTP should not be seduced by this overly simplistic logic. It ignores what may be enormous differences in the ability of different compounds to release the metal ion in a manner that makes it available to interact with target sites inside the cell nucleus. In our view, NTP made this mistake when it lumped soluble nickel compounds into the undifferentiated category of "nickel compounds," which it then proceeded to classify as a "known human carcinogen." A more nuanced understanding of species-specific differences would have resulted in a less severe classification for soluble nickel.